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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/556,803 | 11/14/2005 | Giuseppe Arpaia | 279737US0PCT | 1463 |

22850 7590 08/06/2010

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| EXAMINER | |
|---|---|
| XU, XIAOYUN | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1797 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 08/06/2010 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/556,803 | ARPAIA ET AL. | |
| | Examiner | Art Unit | |
| | ROBERT XU | 1797 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *30 June 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *15-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

1. In view of the appeal brief filed on 06/30/2010, PROSECUTION IS HEREBY REOPENED. The examiner withdraws the finality of the previous Office action and maintains rejections established in the previous Office action as set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

/Vickie Kim/

Supervisory Patent Examiner, Art Unit 1797

***Claim Objections***

2. Claim 15 is objected to because of the following informalities: Claim 15 recites "100 g/ml". The correct word should be "100 µg/ml", because only 100 µg/ml of Pluronic F68 (Poloxamer 188) is supported by the specification (see page 11, line 20). Based on Applicant's remark, 100 g/ml must be a type error. Appropriate correction is required.

***Claim Rejections - 35 USC § 103***

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. **Claims 15 -17** are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoffman et al. (US 2002/0165146) (Hoffman) in view of Katakam et al. (Pharmaceutical Development and Technology, 1997) (Katakam).

In regard to claim 15, Hoffman teaches a method of chromatographic analysis of follicle stimulating hormone (FSH) protein in a sample for quantifying the total FSH protein. The method comprises:

performing chromatography on the protein sample (see paragraph [0083]); and

manipulating data to determine the quantity of the total FSH protein (see paragraph [0083]).

Hoffman teaches that pharmaceutically acceptable solubilizers such as, Pluronic F68 or poloxamer 188 may optionally be added to FSH solution to reduce aggregation (see paragraph [0100]). Using ultra pure water as solvent for surfactant solution is a common practice in the art. At time of the invention it would have been obvious to one of ordinary skill in the art to prepare the protein sample by adding poloxamer 188 in ultra pure water to the sample in order to reduce aggregation during chromatography purification.

Hoffman does not specifically teach the concentration of Poloxamer 188 being 100 µg/ml. Katakam teaches the use of Poloxamer polymer to stabilize recombinant human growth hormone (rhGH) against various processing stress (see title). Katakam tests various concentrations of Poloxamer 188 (Pluronic 68) in the range from 0.001% (below cmc) to 0.2% (above cmc) (see Table 1). The concentration of 100 µg/ml is equivalent to 0.01%. Katakam's teaching meets the recited limitation.

Katakam teaches that: "since surfactants adsorb preferentially at the air/water interface, they are believed to minimize aggregation by reducing the adsorption of protein at interfaces. As a surfactant forms a complete monolayer at the surface at its critical micelle concentration (cmc), the protection is expected to be linked to the cmc value" (see page 146, left col. 1st paragraph). Katakam further gives examples: (1) "at a concentration of 0.2%, which was higher than the cmc of all poloxamers, the aggregation of rhGH was prevented by all poloxamers as evidenced by the lack of absorbance at 400nm as well as SEC-HPLC assay"; (2) "Below and at cmc, only Poloxamer 407 was found to be effective" (see page 146, left col. 1st paragraph). Thus, ordinary skill in the art would have learned that cmc is a critical concentration that needs to be exceeded in order to form a complete monolayer at the surface of micelle. The

0.01% of Poloxamer 188 is twice of cmc (0.0055%) needed for the surfactant to form a complete monolayer on the surface of micelle as taught by Katakam. Therefore, at the time of the invention it would have been obvious for a routineer to try 0.01% of Poloxamer 188 first, because it would save money and cause no harm to protein by trying low concentration of surfactant first.

Katakam teaches that surfactants (poloxamer) adsorb preferentially at the air/water interface, they are believed to minimize aggregation by reducing the adsorption of protein at the interface (see page 145, right col. last paragraph). Katakam teaches that surfactant forms a complete monolayer at the surface of protein at its critical micelle concentration (cmc), the protection is expected to be linked to the cmc value (see page 146, left col. 1st paragraph). Here, Katakam teaches that the protection is a result of surfactant forms a monolayer on the surface of the protein. The mechanism is universal to all proteins. Katakam cites Thurow et al. that poloxamers prevent both the adsorption of dissolved proteins to hydrophobic interfaces and the resultant aggregation (see page 146, left col. 1st paragraph). Therefore, Katakam teaches that surfactant can minimize aggregation of proteins in general, and HGH in particular. HGH has 200 amino acid and molecular weight of 22 KDa. FSH has 202 amino acid and molecular weight of 22 KDa. Katakam cites that Thurow et al has shown that for low molecular weight peptides (proteins), surfactants with short side chain seem to be suitable for stabilization, for high molecular weight proteins, surfactants with longer side chain stabilize better (see page 146, left col. 1st paragraph). Since HGH and FSH have about the same molecular weight, same kind of surfactant should work well on both of them.

Hoffman does not specifically teach using data from calibration with a standard to calculate the quantity of the protein. However, using data from calibration with a standard to calculate the quantity of the protein is well known in the art. At time of the invention, it would have been obvious for a person of ordinary skill in the art to use data from calibration with a standard to calculate the quantity of the protein.

In regard to claim 16, simple dilution of protein sample to a level acceptable for the chromatographic system is well-known in the art.

In regard to claim 17, Hoffman teaches using size-exclusion chromatography to purify FSH (see paragraph [0083]).

***Response to Arguments***

5. Applicant's arguments with respect to claims 15-17 have been considered but are moot in view of the new ground(s) of rejection.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT XU whose telephone number is (571)270-5560. The examiner can normally be reached on Mon-Thur 7:30am-5:00pm, Fri 7:30am-4:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Vickie Kim can be reached on (571)272-0579. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

RX
/Vickie Kim/
Supervisory Patent Examiner, Art Unit 1797